

# PENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:  
**DU PONT PHARCEUTICALS  
COMPANY**  
**Attn. O'BRIEN, M.**  
**Legal/Patent Records Center**  
**1007 Market Street**  
**Wilmington, Delaware 19898**  
**UNITED STATES OF AMERICA**

# PCT

## NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

<p>Applicant's or agent's file reference <b>DM6919</b></p> <p>International application No. <b>PCT/US 99/ 00747</b></p> <p>Applicant <b>DU PONT PHARMACEUTICALS COMPANY</b></p>	<p>Date of mailing (day/month/year)      <b>01/09/1999</b></p> <p><b>FOR FURTHER ACTION</b>      See paragraphs 1 and 4 below</p> <p>International filing date (day/month/year)      <b>14/01/1999</b></p>
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1.  The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

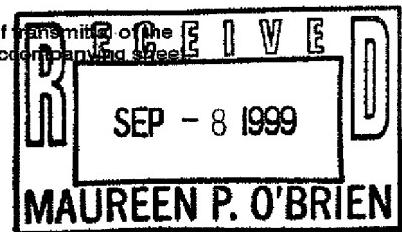
**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmission of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.



2.  The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

<p>Name and mailing address of the International Searching Authority</p> <p>European Patent Office, P.B. 5818 Patentlaan 2      NL-2280 HV Rijswijk      Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,      Fax: (+31-70) 340-3016</p>	<p>Authorized officer</p> <p><b>Claudia Aragone</b> </p>
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## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>DM6919</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/00747</b>	International filing date (day/month/year) <b>14/01/1999</b>	(Earliest) Priority Date (day/month/year) <b>14/01/1998</b>
Applicant <b>DU PONT PHARMACEUTICALS COMPANY</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

**PREPARATION OF A LIPID BLEND AND A PHOSPHOLIPID SUSPENSION CONTAINING THE LIPID BLEND, AND CONTRAST AGENTS BASED ON THESE**

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 99/00747

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 1-44 in part because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

**1. Claims: 1-23 in part, and 36-44**

The process for preparing a phospholipid suspension as described in claims 1-23, and the phospholipid suspension thus obtained.

**2. Claims: 1-23 in part, and 24-28**

The process for preparing a perfluorocarbon-containing contrast agent according to these claims.

**3. Claims: 29-35**

The process for the preparation of a lipid blend according to these claims.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-44 in part

In view of the large number of compositions, which are defined by the general definition in the claims, the search had to be restricted for economic reasons. The search was limited to the compositions for which pharmacological data was given and/or the compositions mentioned in the claims, and to the general idea underlying the application (see guidelines, Chapter III, paragraph 2.3).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/00747

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 A61K9/127 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 349 429 A (CENTRE NAT RECH SCIENT) 3 January 1990 (1990-01-03) examples claim 1 ---	1-28, 36-44
Y	US 5 637 289 A (KLAVENESS JO ET AL) 10 June 1997 (1997-06-10) example 5 ---	1-28, 36-44
Y	WO 95 32006 A (IMARX PHARMACEUTICAL CORP) 30 November 1995 (1995-11-30)	1-28
X	examples 1-3 ---	36-44
P, Y	WO 98 47487 A (DUMEX LTD AS ;NIELSEN LISE SYLVEST (DK)) 29 October 1998 (1998-10-29) page 66 - page 67 ---	1-28
P, X	---	1,17-23
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 August 1999

Date of mailing of the international search report

01.09.99

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Dullaart, A

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/00747

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 31196 A (IMARX PHARMACEUTICAL CORP) 10 October 1996 (1996-10-10)	1-35
X	example 1 ---	36-44
Y	G. GREGODIADIS (EDITOR): "Liposome Technology, Volume 1: Preparation of Liposomes" 1984 , CRC PRESS, INC. , BOCA RATON, US XP002101586 13391 page 29 - page 35 & D.W. DEAMER: "PREPARATION OF SOLVENT VAPORIZATION LIPOSOMES" ---	1-23
Y	OHKI K ET AL: "SHORT AND LONG RANGE CALCIUM-INDUCED LATERAL PHASE SEPARATIONS IN TERNARY MIXTURES OF PHOSPHATIDIC ACID PHOSPHATIDYLCHOLINE AND PHOSPHATIDYLETHANOLAMINE" CHEMISTRY AND PHYSICS OF LIPIDS, 1989, VOL. 50, NO. 2, PAGE(S) 109-118., XP002101581	1-44
X	abstract page 110, left-hand column page 113; figure 4 page 117 ---	36-44
A	MARUYAMA KAZUO ET AL.: "Prolonged circulation time in vivo of large unilamellar liposomes composed of distearoyl phosphatidylcholine and cholesterol containing amphipathic poly(ethylene glycol)." BIOCHIMICA ET BIOPHYSICA ACTA, 1992, VOL. 1128, PAGES 44-49, XP002101582 table 1 figures 1-3 ---	1-28, 36-44
A	BEDU-ADDO FK ET AL: "Effects of polyethyleneglycol chain length and phospholipid acyl chain composition on the interaction of polyethyleneglycol-phospholipid conjugates with phospholipid: implications in liposomal drug delivery." PHARM RES, MAY 1996, VOL. 13, NO. 5, PAGE(S) 710-717, XP002101583 paragraph 'RESULTS' ---	1-28, 36-44
		-/-

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/00747

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	BELSITO S. ET AL: "Sterically stabilized liposomes of DPPC/DPPE-PEG:2000. A spin label ESR and spectrophotometric study" BIOPHYSICAL CHEMISTRY, 5-10-1998, VOL. 75, NO. 1, PAGE(S) 33-43, XP002101584 figure 1 figures 5,6; table 2 ---	1-28, 36-44  29-35
A	NIKOLOVA AN ET AL: "Effect of grafted PEG-2000 on the size and permeability of vesicles." BIOCHIM BIOPHYS ACTA, 22-11-1996, VOL. 1304, NO. 2, PAGE(S) 120-128, XP002101585 the whole document ---	1-23, 36-44
Y	WO 96 08234 A (IMARX PHARMACEUTICAL CORP) 21 March 1996 (1996-03-21)	1-28
X	examples ---	36-44
P,Y	WO 98 10799 A (IMARX PHARMACEUTICAL CORP) 19 March 1998 (1998-03-19)	1-28
P,X	example 1 ---	36-44
Y	WO 96 40285 A (IMARX PHARMACEUTICAL CORP ;UNGER EVAN C (US); SHEN DEKANG (US); WU) 19 December 1996 (1996-12-19)	1-28
X	example 6 ---	36-44
P,Y	WO 98 51284 A (IMARX PHARMACEUTICAL CORP) 19 November 1998 (1998-11-19)	1-28
P,X	example 12 ---	36-44
Y	WO 97 40858 A (IMARX PHARMACEUTICAL CORP) 6 November 1997 (1997-11-06)	1-28
X	examples ---	36-44
Y	WO 95 15118 A (MATSUMAGA TERRY ;UNGER EVAN C (US); YELLOWHAIR DAVID (US)) 8 June 1995 (1995-06-08)	1-28
X	page 25 examples claims 19,20 ---	29-44
E	EP 0 901 793 A (IMARX PHARMACEUTICAL CORP) 17 March 1999 (1999-03-17) examples 1,2 -----	1-28, 36-44

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

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**INTERNATIONAL SEARCH REPORT**

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In. International Application No

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 99/00747

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